Prostate

Prostate

Prostatitis

- Clinical Features :-
  - dysuria, frequency, lower back pain, poorly localised suprapubic or pelvic pain
  - on PR examination → enlarged + tender prostate
    (specially in acute → local symptoms + fever + leukocytosis)

① Acute Bacterial Prostatitis

- mostly E. Coli, and other gram-negative organisms
- tender + painful (+ Fever + leukocytosis)
- Concominant infection of the urethra and bladder
  ↳ reach prostate by :- 1- direct extension
  2- vascular channels (more distal sites)
- * Histopathology :- - Congestion, edema, acute inflammatory infiltrate
  progression of disease ↓
  destruction of glandular epithelium → microabscesses
- Grossly :- visible abscesses (uncommon, develop in extensive tissue destruction, ex: DM)

② Chronic Prostatitis

- may follow acute prostatitis or develop insidiously
- * most cases → Chronic abacterial prostatitis → only ↑ in WBC in prostatic secretions
  Some cases → Chronic bacterial prostatitis → ↑ in WBC + bacteria in prostatic secretions
- Histopathology :- non-specific features → lymphocytic infiltrate, glandular injury, fibroblastic proliferation, acute inflammatory changes

Even if asymptomatic → UTI organism reservoir → important recurrent UTI cause in men

③ Granulomatous Prostatitis

- with systemic inflammatory processes (TB, Sarcoidosis, fungal infections)
- * non-specific reaction to inspissated prostatic secretions and after TUR (transurethral resection) of prostate

PR = Per-Rectal Examination

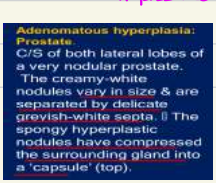
Tumors / Lesions

- normal prostate is divided into zones (periurethral, central, transitional, peripheral)
  - ↳ important to differentiate the zones, as hyperplasia and malignancy occur in different zones
- 70 - 80 % Carcinomas ⟶ peripheral zones
- most NH lesions ⟶ central and inner transitional zones

① Nodular Hyperplasia (NH) of the Prostate (P)

- Common abnormality, rises progressively with age (90% by the 8th decade)
- proliferation of both stromal + epithelial elements ⟶ enlargement of P ⟶ UT obstruction
- Pathogenesis ⟶ **Androgens** have central role in development :-
  - does not occur in male castrated before puberty, or in men with genetic diseases blocking androgen activity ⟿ long time ago slaves were castrated to prevent it
  - **DHT** (dihydrotestosterone) androgen derived from testosterone by 5α-reductase and it's metabolite 3α-androstanediol ⟶ major hormonal stimuli for stromal + glandular proliferation in men with NH
    - ↳ DHT binds to nuclear androgen receptor ⟶ Synthesis of DNA, RNA, GFs, ... other ⟶ hyperplasia ⟿ use of 5α-reductase inhibitors for treatment of symptomatic NH
- Morphology :-
  - in the **inner, periurethral glands** of P, i.e **above the verumontanum**
  - enlarged P (300 gm+)
  - well-circumscribed nodules bulging from cut surface in the inner (central + transitional) regions
  - nodules maybe solid, or contain cystic spaces
  - urethra is compressed (**slit-like orifice**)
- Microscopically :-
  - hyperplastic glands lined by **dual (double) cell population**
  - Central tall columnar epithelial cells ⟶ crowding ⟶ **papillary projections**
  - peripheral layer of flattened basal cells
  - inspissated, proteinaceous secretory material in glandular lumina ⇒ **Corpora amylacea**

- NH ⟶ double layers
- malignancy ⟶ single layer + prominent nucleoli



Adenomatous hyperplasia: Prostate. C/S of both lateral lobes of a very nodular prostate. The creamy-white nodules vary in size & are separated by delicate greyish-white septa. ‖ The spongy hyperplastic nodules have compressed the surrounding gland into a "capsule" (top).

- Clinical manifestations :-
  - occure in only 10 % of men with disease
  - lower UT obstruction (hesitancy, intermittent intruption of urinay system while uriating)
  - Complete UT obstruction ⟶ painful bladder distention ⟶ bilateral hydronephrosis + RF
  - urgency, frequency, nocturia ⟶ bladder irritation
  - Complete obstruction + residual urine in bladder ⟶ ↑ UTI risk

(2) Prostatic Carcinoma (Pca)

* - most common visceral cancer in males, 2nd (after lung ca) most common cause of cancer related deaths men > 50 years old

* - latent Pca > clinically apparent Pca

- unKnown Cause, but clinical and experimental observations suggest hormones, genes, environment (pathogenesis) :-

1- Hormones : (androgen contibution to Pca development suggestion)
  - does not develop in males castrated before puberty
  - growth of many Pca can be inhibited by orchiectomy or estrogen administration (ex : DHT)

2- Hereditary :
  - ↑ Pca risk in first degree relatives of Parents with Pca

3- Racial :
  - Symptomatic more common, occurs at earlier ages in American Blacks

4- Genes :
  - Overexpression of 2 ETS family transcription factors (also involved in Ewing Sarcoma)
  * - inhirited BRCA 1 and BRCA 2 mutations (especially BRCA 2) ⟶ ↑ Pca risk
  - men with lynch syndrome (HNPCC) ⟶ ↑ Pca risk

5- Environmental influences :
  - ↑ risk in certain industial settings and geographic differences
  - migration from low-risk to high-risk ares maintain low-risk
  - diet high in animal Fat ↑ risk

* - detected on the basis of elevated plasma levels of prostate specific antigen PSA > 4 ng/mL but tissue biopsy is standard to confirm Pca (because men without Pca have ↑ PSA such as NH and prostatitis cases)

- Grossly :-
  - 70 - 80 % → prostate peripheral zone
  - palpable as irregular hard nodules by PRE
  - Pca is less likely to cause Urethral obstruction than NH
  - Early Pca → hard, ill-defined, subscapular masses, CIS → from grey-white to yellow lesions infiltrating adjacent gland
  - locally advanced Pca → infiltrate : (1) peiurethral zones (2) Seminal vesicles (3) invade bladder wall
  - Denonvilliers fasca prevents gowth of Pca posteiorly (infrequent rectum invation of Pca)
  - metastasis to regional LN may occur early (external + internal iliac → para-aortic)
- Microscopically :-
  - most are adenocarcinomas with variable degrees of differentiation
  - small glands infiltrating adjacent strama in irregular haphazard fashion
  - due to scant strama Pca lie back to back
* - lined by single cuboidal cell layer and absence of basal cell layer
  - conspicuous / prominent nucleoli
  - ↑ anaplasia degrees, irregular ragged glandular structures, papillary or cribiform epithelium
  - extreme cases → sheets of poorly differentiated cells

* - NH does not transform into Carcinoma but NH + Cancer may be present together
- PIN (prostatic intraepithelial neoplasia) has been suggested as pobable Pca precursor.
  ↳ subdivided into high and low grade patterns → high-grade PIN shows molecular changes with invasive Pca
- Pca histologic grading through Gleason System (1-5 degrees) based on :
  (1) degree of glandular architecture (2) differentiation (3) nuclear anaplasia (4) mitotic activity
- Clinically :-
  1- Silent → early stages, 10% of localized Pca are unexpectedly discoved (30% → 30-40 years old)
  most begin in peripheral regions → discoved duing routine PRE
  2- Extensive disease may produce prostatism
  3- Evidence of metastasis (uncommon mode of presentation)
  ↳ Bone metastasis (axial skeleton) are common and may cause osteolytic or osteoblastic (more common) (presence in older male → advanced Pca) lesions

-Prostatism
↳ local discomfort and evidence of lower UT obstruction with hard gland Prostate on PRE

- its important to differentiate between high-grade prostate adenocarcinoma (PAC) involving the urinary bladder and high-grade urothelial carcinoma (UC) infiltrating the prostate (which one is the primary / main cancer ? ⟶ markers are used)

* - Prostatic and urothelial markers :-

1- PSA
2- NKX3.1
⟶ positive for PAC

3- GATA 3
4- high molecular weight cytokeratin
⟶ positive for UC

5- P63
6- thrombomodulin

* - prostate specific antigen (PSA) and prostate acid phosphatase (PAP)

⟶ assist in verifying prostatic linage in cases of metastatic carcinoma of unknown origin

⟶ sensitivity ↓ in poorly differentiated carcinomas

PSA ⟶ diagnosis of early Pca (serum level 4 ng/L ⟶ upper normal limit)

⟶ diagnostic value enhanced when used in conjuction with other procedures

ex : (1) PRE (2) transrectal sonography *(3) needle biopsy (most reliable)

⟶ monitoring after treatment (↑ after ablative therapy = recurrence ± metastasis)

* - Staging :-

Table 18-3 TNM Staging of Prostatic Adenocarcinoma:

T1-Clinically **Inapparent** Lesion By Palpation/Imaging Studies
T1a -Involvement of ≤5% of resected tissue
T1b -Involvement of >5% of resected tissue
T1c -**Ca present on needle biopsy**(following elevated PSA)

T2-Palpable Or Visible Cancer Confined To Prostate
T2a -Involvement of ≤50% of one lobe
T2b -Involvement of >50% of one lobe, but unilateral
T2c -Involvement of both lobes

* T3-Local Extraprostatic Extension
T3a-Extracapsular extension
T3b-Seminal vesical invasion

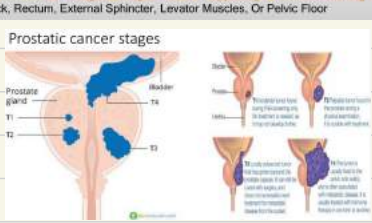
T4-Invasion of Contiguous Organs And/Or Supporting Structures Including Bladder Neck, Rectum, External Sphincter, Levator Muscles, Or Pelvic Floor

Status of Regional Lymph Nodes (N)

N0 -No Regional LN Metastases N1
-Metastasis In Regional LN

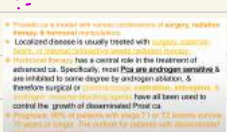
Distant Metastases (M)
M0 -No Distant Metastases
M1 -Distant metastases present

❑ Anatomic staging of **Pca** (by clinical examination, surgical exploration, radiographic imaging techniques) &, in some systems, & the histologic **grade** of the T & levels of T markers has an important role in the evaluation & treatment of Pca & correlate well with prognosis.



- Prognosis :-
  - 90 % T1 or T2 Stages survive 10 years longer
  - outlook for disseminated disease remains poor

- Treatment :-



(ما رح تسال عنه)

Female

Vulvar Diseases

non-neoplastic — neoplastic

- less common
- SCC (mostly)

- Vulva has moist hair-bearing skin and delicate membrane
  - ↳ prone to inflammations, and dermatologic disorder caused by non-specific microbes
- Intense itching + Scratching → exacerbate primary condition
- 5 most important forms of vulvar infection related to STD (in North America) :-
  1- HPV (16, 18 → cervical cancer) (6, 11 → warts)
  2- HSV (herpes genitalis) → vesicles
  3- Gonococcal suppurative inflammation
  4- Syphilis
  5- Candida Vulvitis → mostly impacts females if pregnant, or immune compromised, or is diabetic

* Contact Dermatitis
- most common cause of vulvar pruritus
- reactive inflammation to exogenous stimulus
  - irritant contact dermatitis → to irritant
  - Allergic contact dermatitis → to allergen

→ Both present as well-defined erythmatous weeping + Crusting papules + plaques
- ↳ acute spongiotic dermatitis
- ↳ Subacute dermatitis with epithelial hyperplasia

- Can occur in child wearing diper
  - ↳ pee on themself → allergy + fungal infection
    - ↳ solution : change diper + cream

Non-neoplasic Vulvar Diseases

(1) Lichen Sclerosus

- in postmenopausal women, elderly female
- Smooth white plaques + thinned out skin
- microscopically :-
  - epidermis thinning
  - disappearance of rete pegs
  - hydropic basal cell degeneration

* - not pre-malignant lesion, but 15 % ⟶ develop SCCa

(2) Lichen Simplex Chronicus

- end result of inflammatory condition
- appears as leukoplakia area
- microscopically :-
  - hyperKeratosis + hypergranulosis + acanthosis
  - epithelin -> no atypia
  - leukocytic infiltration of dermis

* - no ↑ cancer predesposition, but can be present at margins of adjacent cancer

* Both lichen Sclerosis + Lichen Simplex Chronicus

⟶ non-neoplastic epithelial disorders

⟶ may co-exist in different areas

⟶ may appear grossly as depigmented white patches (leukoplakia)

(3) Condyloma Accuminatum

Tumors

① Condylomas → Benign Tumors

- 2 distinctive biologic forms :-

1- Condyloma lata – occur in secondary Syphilis – not commonly seen today

2- Condyloma acuminate

- papillary
- multiple, red-pink to brown on Vulva
- more common

* - Anogenital warts (HPV 6, 11)

* - Hallmark : Koilocytosis

- not precancerous by itself

Neoplastic Vulvar Diseases

① Vulvar Intraepithelial Neoplasia (VIN)

- high grade VIN = II or III (VIN III → Carcinoma in situ)
- multiple foci, or coexist with invasive lesion
- may be present for years before cancer progression
- genetic, immunologic, environmental influences determine the course
  - ↳ Smoking, Super-infection of new HPV strains

② Carcinoma of the Vulva

- Caused by HPV 16, 18
- 3% of genital tract cancers in women
- > 60 years old
- 90% → SCC

③ Squamous Cell Carcinoma (SCC)

1. Basaloid or poorly differentiated SCC ⇝ most common
   - younger women
   - HPV 16, 18 related, lesions in Vagina or Cervix
   - poorly differentiated cells

2. Well-differentiated SCC ⟶ less common

- older women
- * - Not HPV related → So it lacks typical cytologic changes of VIN
- well to moderately differentiated cells
- adjacent to lichen simplex or sclerosis

(4) Extramedullary Paget Disease

- intraepithelial Carcinoma
- non-demonstratable underlying Ca. (unlike breast)
- presentation: red, scaly, crusted plaque or inflammatory dermatosis
- microscopically:
  - large malignant epithelioid cells
  - granular cytoplasm
  - * - Cytoplasmic vacules containing mucin (PAS +)
  - when confined to epidermis → persist years without invasion

Vagina

Vaginitis

- Common → producing vaginal discharge (Leukorrhea)
- may represent normal commensals that become pathogenic
  - DM
  - * Antibiotic therapy (disrupts normal flora) → common
  - after abortion or pregnancy
  - elderly with compromised immunity
  - AIDs

(1) Candidal (monilial) vaginitis

- Curdy-white discharge
- appearance of symptomatic infection involves :-
  - predisposing influences
  - Sexual transmission of new more agressive strain
  - 2 types :-

1- uncomplicated Thush

- Cause : Candida albicans
- Single episode or < 4 episodes in a year
- mild-moderate symptoms

2- Complicated Thush

- 4 + episodes a year
- Severe symptoms
- Pregnancy, Poorly Controlled DM immune deficiency

(2) Trichomonas Vaginalis (T. Vaginalis)

- watery copious grey-green discharge
- Parasite identified microscopically

(3) Non-Specific atrophic Vaginitis

- in post menopausal women, with pre-existing mucosal atrophy

Vaginal Neoplastic Diseases

* Vaginal clear cell Adenocarcinoma
  - young women (late teens – early 20s)
  * - mothers took diethylstilbestrol during pregnancy
  - sometimes do not appear until 3rd - 4th decades
  - 1/3 → arise in cervix

Cervix

- Barier to entrance of air and microflora, permits the escape of menstrual flow + Capable of dilating (Birth)

Cervicitis

- Predisposing factors
  - trauma
  - Excessive secretion
  - high / low estrogen levels
  - alkaline media of cervical canal during ovulation
- extremely common
- mucopurulent to purulent vaginal discharge
- Cytologic examination of discharge ⟶ WBC + inflammatory atypia of sheed epithelial cells ± microorganisms

*
- post coital bleeding ⟶ Serious ⟶ maybe Cancer
- Endocervical canal (lined by endocervical glands) + Ectocervix (lined by squamous epithelium) ⟶ point of meeting "squamocolumnar junction" ⇝ HPV target point

(1) Acute Cervicitis

- Child birth, STD (gonorrhea)
- often confused with vaginitis

(2) Chronic Cervicitis

- persistent discharge for 3 months
- associated with :-
  - leukorrhea, destruction of stratified columnar epithelium of ectopic cervix
  - growth of columnar epithelial endocervix ⟶ cervical erosion (reddening of ectocervix)
  - ectocervix Granularity, Development of nabothian cyst, Endocervical polyp
- if caused by organisms ⟶ move up into uterus + fallopian tubes ⟶ pelvic inflammatory disease (PID) ⟶ infertility and peritonitis
  - or - organisms can be passed to sexual partners ⟶ serious complications

- Grossly nonspecific cervicitis can be either :-
  1- Acute non-specific cervicitis
    - uncommon , limited to postpartum women
    - Caused by staphylococci or streptococci
  2- Chronic non-specific cervicitis
    - Common , nearly ubiquitous , ever-present entity
- Overgrowth of regenerating squamous epithelium → blocks endocervical gland orifices in transformation zone → small Nabothian cysts lined by mucus-secreting columnar epithelium

lesions

- these were also associated with Chronic cervicitis (*{)

① Cervical Ectropion ⇝ Cervical erosion (not actual cell erosion occurs)
- eversion of endocervix exposing columnar epithelium to vaginal milieu
- normal physiological condition , seen in :-
  - cervical examination in adolescents
  - pregnancy
  - women taking estrogen containing contraceptives
- thought to be induced by ↑ estrogen levels , does not represent metaplasia

② Nabothian cyst
- mucus-filled cyst
- appear as fim bumps on cervix surface
- Stratified squamous epithelium of the ectocervix grows over the simple columnar epithelium of the endocervix
- tissue growth → block cervical crypts → trapping cervical mucus inside the crypts
- resolve on their own , if occur with Chronic cervicitis → underlying inflammation cause must be treated

3 Endocervical Polyp

- inflammatory lesion, protrude as polypoid mass through exocervix (not a tumor)
- large, soft, smooth, glistening surface
- underlying cystically dilated spaces filled with mucinous secretion
  → rounded, soft, sessile gelatinous polyp fills endocervical canal
- no malignant potential

Tumors

1 Cervical Intraepithelial Neoplasia (CIN)

- graded depending on extent of epithelial involvement :-
  - CIN I : mild dysplasia (< 1/3 of full epithelial thickness) — Can be reversible
  - CIN II : moderate dysplasia (2/3 of full epithelial thickness) — Can be reversible
  - CIN III : severe dysplasia (full epithelial thickness, carcinoma in situ)

- Dysplastic changes :-
  - High N/C ratio
  - Regular nuclei
  - Atypia
  - Mitotic figures
  - Irregular nuclear contours

- Epidemiology and Pathogenesis :-
  - CIN → 30 year olds, invasive cancer → 45 years old (peak incidence)
  - HPV detected in precancerous lesions and invasive neoplasms
    ↳ high risk types (16, 18, 31, 45) → majority of cervical cancers
    ↳ integrate into host genome → express large amounts of E6 + E7 proteins → block / inactivate P53 and RB respectively
    → HPV vaccine effective in preventing HPV infections → cervical cancers
  - all invasive cervical SCC arise from precursor CIN, but not all CIN progress into invasive cancers and persist without change or regress
  - Cytological examinations can detect CIN before gross abnormalities
    follow-up revealed that :-
    (1) precancerous CIN may precede development of overt cancer by many years / decades
    (2) fraction of CIN cases progress to invasive cancer
  - precancerous CIN may begin as :- (1) low-grade progress to higher grade
    (2) high grade arise de novo

depending on : (1) location of HPV infection in transitional zone (2) type of HPV (3) host factors

* opposite of endometrial cancer that occurs in post menopausal women

- important risk factors for CIN and invasive cancer development :-

1- Early age at first intercourse
2- multiple sexual partners
3- male partner with previous sexual partners
4- persistent high-risk HPV infection
5- lower socioeconomic groups
6- multiple pregnancies
7- rarity among virgins

* → when treating patient must also treat partner

* - Morphology :-

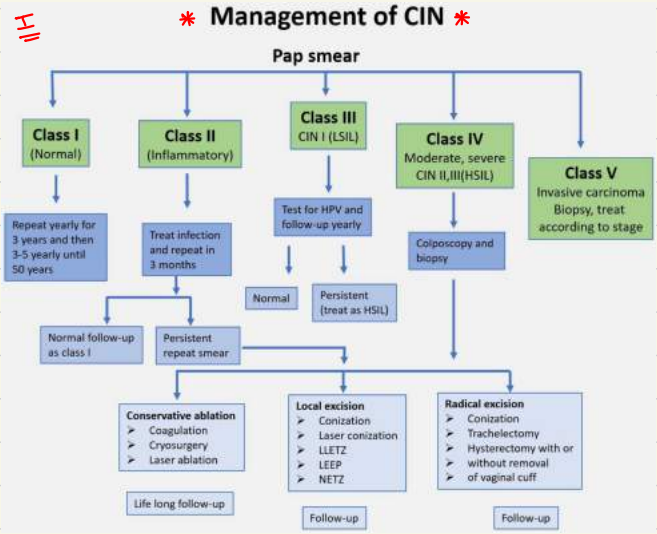
(1) CIN I → mild dysplasia, Koilocytosis, composed of nuclear hyperchromasia and angulation with perinuclear vacuolization (halo)

(2) CIN II → 1- maturation of Keratinocytes
2- cell + nuclear size pleomorphism, heterogeneity of nuclear chromatin
3- mitosis above basal layer, superficial layer shows some differenciation

(3) CIN III → greter pleomorphism, marked hyperchromasia, disorderly orientation of cells, loss of maturation,

with time : (4) → dysplastic changes become more atypical, but alterations are confined to epithelial layers and it's glands → Carcinoma in situ

(5) → Invasive carcinoma (not definite change, no inevitability to this progression)



HPV Related Disease

- Genital warts
- CIN→Cervical Cancer
- VIN → Vulvar Cancer
- VaIN → Vaginal Cancer
- AIN → Anal Cancer
- PIN → Penile Cancer
- Recurrent Laryngeal Papillomatosis
- Head&Neck Cancers

(2) Cervical Cancer

- Most common → SCC → peak incidence at 45 years (10-15 years after detection of their precursor: CIN)
- Only reliable way to monitor disease → Carful follow-up + repeat biopsies
- Grossly :-
  - develop in transformation zone
  - * range from invisible microscopic foci to visible exophytic (polypoid, infiltrating) penetrating underlying stroma → barrel cervix (identified by palpation)
  - extension into parametrial soft tissue → fix uterus to pelvic structures
  - Spread to pelvic LN determined by :- (1) depth (<1% → T<3mm, >10% → T>5mm)
    (2) presence of capillary lymphatic invasion
  - invasion to adjacent structures + distant metastasis → late in disease
  - * Graded 1-3 → based on cellular differentiation / Staged 1-4 → depending on clinical spread
- Clinical aspects :-
  - pap smear ↑ proportion of early diagnosis (stage 1)
  - most are diagnosed in preinvasive phase, appear as white areas on colposcopy
  - Advanced cases seen in :- (1) never had a Pap smear
    (2) waited many years since prior smear
    - Cause unexpected → vaginal bleeding, leukorrhea, dyspareunia (painful coitus), dysuria,
    - * post coital bleeding

* - Post coital bleeding → treated as cervical cancer till proven otherwise (ex: infection)
- post menopause bleeding → treated as endometrial cancer till proven otherwise

- * Staging :-

- Treatment :- (ما رح تسأل عنه)
  - CIN → laser or cone biopsy
  - invasive → surgical excision
- Prognosis (5 year survival rate) :-
  - Stage 0 (preinvasive) → 100%
  - Stage 1 → 85%
  - Stage 2 → 65%
  - Stage 3 → 35%
  - Stage 4 → 7%

- Prevention :-
  - HPV vaccine
  - Detection of precursors and their eradication (cone biopsy or laser vaporization) ← most effective method

Uterus

Disease of the Uterus

(1) Puerperal Sepsis (acute suppurative inflammation of uterus following labor or abortion)

* - Fever during 2 weeks post labor / abortion → puerperal sepsis till proven otherwise
- Caused by pyogenic bacteia (E.coli, Streptococcus)
- Complication :- - Toxemia - Septicemia - Peritonitis
  - Pyemia - Septic thrombophlebitis
* - Symptoms :- - UTI - Infection / inflammation of breast tissue
  - Endometritis - Wound infection at surgical site
  - Septic pelvis thrombophlebitis - Fever ≥ 100.4° within 10 days of delivery
- give IV antibiotic in very sever cases

(2) Endometritis (inflammation of the endometrium)

- Causes :- (1) PID (2) miscarriage or delivery (3) Intrauterine device (IUCD)
- Clinically :- - menstrual abnormalities - abdominal pain + pelvic pain
  - Fever - infertility / ectopic pregnancy (due to Fallopian tube damage)

1- Acute Endometritis

- due to N. gonorrhoeae or C. trachomatis
* - neutrophilic cell response

2- Chronic Endometritis

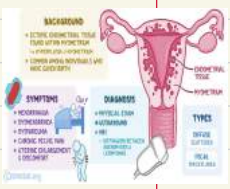
- due to Chlamydial and Mycoplasma
* - lympho-plasmacytic cell response
* - diagnosis requires presence of plasma cells in endometrium

3- TB Endometritis

- with TB salpingitis and peritonitis

- Treatment :- - removal of cause
  - antibiotics
  - Dilation and Curettage (D&C)

③ Adenomyosis (growth of basal layer of endometrium down to myometrium)



- Endometrial stroma, glands (both) embedded in myometrium
- derived from stratum basalis, no cyclical bleeding
- Thick uterine wall, enlarged uterus
- Produce :- - postmenstrual menorrhagia - pelvic pain
  - dysmenorrhea (painful menses) ⇝ enlarged uterus ⟶ exaggerated contractions

④ Endometriosis (presence of endometrial glands outside the uterus)

- in 10% of women in reproductive years, 50% of women with infertility
* - Dysmenorrhea, pelvic pain, pelvic blood-filled mass (Chocolate cyst)
- multifocal multiple tissues in pelvis (ovaries, pouch of Douglas, uterine ligaments, tubes, rectovaginal septum)
  distant sites ⟶ umbilicus, LN, lungs .. etc
- Pathogenesis (3 theories) :-
  1- Regurgitation Theory (most accepted)
  - menstrual backflow through tubes and implantation
  2- Metaplastic Theory
  - Endometrial differentiation of coelomic epithelium
  3- Vascular or lymphatic Dissemination Theory
  - explain extrapelvic or intranodal implants
- Grossly :-
* - functioning endometrium which undergoes cyclic bleeding
  ↳ blood collects in abnormal foci (red-blue to yellow-brown nodules/implants)
  Contains functionalis endometrium ⟶ undergoes cyclic bleeding
* - large blood-filled cysts ⟶ Chocolate cysts
* - leakage + organization of blood ⟶ widespread fibrosis
- Consequences :- - infertility - distortion of ovaries
  - sealing of tubal fimbriated ends - fibrosis
* - Diagnosis (find 2 of 3) :- (1) endometrial stroma (CD-10+)
  ↳ 3 needed for confirmation (2) endometrial gland (3) hemosiderin pigment

* - Clinical manifestations (depend on site) :-

(1) intrapelvic bleeding + peri-uterine adhesions ⟶ dysmenorrhea + pelvic pain

(2) Scaring of oviducts + ovaries ⟶ lower abdominal discomfort, sterility

* (3) rectal wall involvement ⟶ Dyschezia (pain on defecation)

(4) uterine + bladder serosa involvement ⟶ Dyspareunia + dysuria

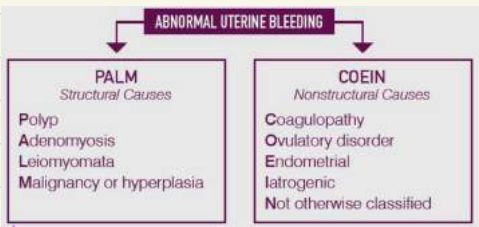
(5) ovarian endometriosis ⟶ Chocolate cyst (pelvic mass)

(5) ⟶

Vaginal bleeding (Blood passes per vagina)

- The most common problem for which women seek medical attention is some disturbance in menstrual function:

(1) Menorrhagia=profuse or prolonged menstrual bleeding
(2) Metrorrhagia= irregular bleeding between the periods,
(3) Ovulatory(intermenstrual) bleeding
(4) Postmenopausal bleeding.
(5) Common causes include endometrial polyps, hyperplasia, ca, leiomyomas, & endometritis.
(6) Vaginal bleeding may also be due to cervical & vagina lesions, such as polyps, cervicitis, or ca.



PALM-COEIN system ⟶ used to classify causes of abnormal bleeding in non-pregnant premenopausal women

(6) Dysfunctional Uterine Bleeding (abnormal bleeding in absence of well-defined organic lesion)

- due to hormonal imbalance
- 4 major causes :-

1 - Failure of Ovulation

- with any dysfunction of hypothalamic-pituitary axis, adrenal, thyroid
- with functioning ovarian lesion (ex: granulosa cell tumor) ⟶ produce excess estrogen
- malnutrition, * obesity, sever physical / emotional stress, debilitating disease
- leads to excess estrogen related to progestrone ⟶ endometrium proliferation not followed by normal secretory phase
- Endometrium shows scant stroma requiring progestrone for support
- poorly supported endometrium ⟶ partial collapse ⟶ rupturing spiral arteries ⟶ bleeding

* - Obesity ⟶ Fat releases estrogen
} adipose tissue processes steroid precursors into estrogens

2- Inadequate luteal phase

- Corpus luteum fail to mature / regress prematurely → lack of progesterone

3- Contraceptive - induced bleeding

- oral contraceptives contain synthetic estrogens + progestin → Endometrial response
- Current / new pills corrected these abnormalities

4- Endomyometrial disorders

- endometrial polyps, Chronic endometriosis, submucosal leiomyomas

(7) Endometrial Hyperplasia (proliferation of endometrial glands → thickening)

- not Cancer, raises the risk of developing endometrial cancer
- any estrogen excess causes it, such as :-
  - failure of ovulation (around menopause)
  - * - estrogen-producing ovarian lesions, ex: → polycystic ovaries (stein-leventhal syndrome)
    → Cortical stromal hyperplasia
    → granulosa-theca cell tumors of ovary
  - Common risk factor → Obesity
  - Exogenous factor → prolonged estrogen administration without balancing with progestin
- Current classification system: - Hyperplasia without atypia
  - Atypical hyperplasia / endometrioid intraepithelial neoplasia (AH / EIN)
- Prior terminologies: - AH / EIN → premalignant condition
  - ↑ risk of progression to / simultaneous endometrial endometrioid adenocarcinoma

* - Essential features :-

- precursor to endometrial endometrioid adenocarcinoma
- ↑ gland : stroma ratio (> 3:1)
- divided into 2 groups → (1) atypia (2) without atypia
  (Complex contour, back to back, scanty stroma) (↳ budding + complex intraluminal contours)
- treatment for AH / EIN → hysterectomy, Progestin therapy (Fertility preservation)
- with time → autonomous proliferation (no need for estrogenic influence) → Carcinoma

Tumors

* Tumors of the Endometrium

(1) Benign Endometrial Polyps

- Sessile or pedunculated, cystically dilated endometrial glands, small muscular arteries, and fibrotic stroma
- monoclonal stromal cells with cytogenic recrangement at 6p21 → neoplastic component of polyp
- no risk for endometrial cancer

(2) Endometrial Carcinoma ~> most common female genital tract cancer

- Common 50-60 year old (uncommon < 40)
- Arise in one of 2 settings :- (1) peimenopausal women with estrogen excess → Endometrioid
  (2) older women with endometrial atrophy → Serous Carcinoma

* 1- Endometrioid Carcinoma (similar to normal endometrium)

- Risk factors (↑ estrogen) :- - Obesity - Prolonged estrogen replacement therapy
  - infertility - estrogen secreting ovarian tumors
- other risk factors :- - DM - HTN
  - Precancerous lesion → atypical endometrial hyperplasia
  - Breast cancer occurs in women with endometrioid Carcinoma (& vice-versa)

- Pathogenesis :-
  - 2nd most common cancer associated with HPNCC → inherited gene defect in DNA mismatch repair gene → microsatellite instability
  - * Mutations in both mismatch repair gene + PTEN → early events occuring in the progression from abnormal proliferation to atypical hyperplasia
  - * lynch syndrome → 60% lifetime risk endometrial carcinoma
    ↳ inherited DNA mismatch repair gene mutations : MLH1, MSH2, MSH6, PMS2, EPCAM
  - Grossly :- - fungating or infiltrative, infiltrating myometrium
    - resemble normal endometrium (mucinous to ciliated to squamous to areosquamous differentiation)

- Grading : I-III , Staging : I -> confined to corpus / II -> cervical involvement / III -> beyond uterus, confined within true pelvis / IV -> distant metastasis or other visceral involvement

* 2- Serous Carcinoma

- no relation with endometrial hyperplasia, not hormone dependent
- (1) arises in atrophy sometimes in setting of an endometrial polyp
- (2) mutations in DNA mismatch repair + PTEN -> rare
- * (3) all cases have mutation in P53
- Grossly :- - small papillae, greater cytological atypia - not graded
  - poorly differentiated, particulary aggressive
- papillary serous carcinoma is strongly dependent on tumor extent, determined by operative staging + peritoneal cytology (very small tumor may spread via fallopian tube to peritoneal cavity)

* - first clinical presentation for all Endometrial cancers -> irregular bleeding (due to erosion, and T surface ulceration)
- prognosis depends on stage
  - ↳ 5 year survival -> Stage I -> 90% , Stage III, IV -> 20%

* Tumors of Myometrium

(1) Lieomyoma (fibroids) (benign smooth muscle cells tumor)

- most common benign tumors in females (30-50% reproductive life)
- Estrogen-dependent (shrink after meopause)
- Grossly : - not encapsulated, sharply circumscibed
  - * - firm grey-white masses - most often multiple (small / massive)
- location : intramural / submucosal / subserosal (may develop hemhorage, cystic changes, calcification)
- larger tumor -> ischemic necrosis (red degeneration) -> seve pain, hemhorage, cystic softening
  - ↳ After menopause -> densely collagenous and calcified

- Clinically : - Asymptomatic or symptomatic
  * - never transform to sarcoma, and does not ↑ malignancy risk
- Cigarette shaped nuclei

(2) Leiomyosarcoma (malignant)

- arise de novo, Solitary tumors
- Grossly : - bulk masses infiltrating uterine wall
  - polypoid lesions
  - soft, hemorrhagic, necrotic, infiltrative borders
- Diagnosis : - Coagulative necrosis - Cytologic atypia - mitotic activity
- Common to recur and metastasize, 5 year survival rate → 40%